REMARKS

I. Preliminary Remarks

The previous obviousness rejections of claims 1-4, 8-11 and 13-14 over Cook (1) (Research Focus, 1996) in combination with Lundin, U.S. 5,558,986 alone; and of claims 1 and 15-18 over those references further in view of Cook (2) (WO 94/264413), have been withdrawn but new rejections based upon those references have been entered. Specifically, claims 1, 2, 4, 5, 8-11 and 13-20 stand rejected over Cook (1) (Research Focus, 1996) in combination with Lundin, U.S. 5,558,986 and claims 6, 7 and 12 stand rejected over those references further in view of Cook (2) (WO 94/264413).

II. Outstanding Rejections

Claims 1-14 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to distinctly claim the subject matter of the invention.

Claims 1, 2, 4, 5, 8-11, and 13-20 stand rejected under 35 U.S.C. §103(a) as being obvious over Cook (Research Focus 1(7): 287-94, 1996) (hereinafter "Cook (1)") in view of Lundin *et al.* (U.S. 5,558,986) (hereinafter "Lundin").

Claims 6-7 and 12 stand rejected under U.S.C. §103(a) as being unpatentable over Cook (1) in view of Lundin, and in further view of Cook (WO 94/26413) (hereinafter "Cook (2)").

III. Patentability Arguments

A. The Rejections Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn

The rejection of claims 1-14 under 35 U.S.C. §112, second paragraph, should be withdrawn for the following reasons. Claim 1 is complete and does not omit any essential elements. It clearly recites the process of i) mixing a cell sample with a cell lysis reagent, ii) mixing the lysed sample with a specific binding partner to perform a specific binding assay by forming a reaction mixture comprising a specific binding partner-analyte complex, iii) mixing the lysed cellular sample with a cyclodextrin sequestrant for the cell lysis reagent, and iv) detecting the presence of the specific binding partner-analyte complex.

Applicant submits that the relationship between specific binding partner, tracer and labeled assay reagent is clear to those of ordinary skill in the art upon reading the disclosure. As discussed at page 14, lines 26-29 of the specification, "[t]he tracer is a labeled assay reagent, which might be the specific binding partner of the analyte or might be another assay reagent." Thus, in example 5, the use of ^{3}H-IP_3 as a tracer in an IP_3 assay is described where IP_3 binding to its receptor is detected by displacement of the ^{3}H-IP_3. In the case of an IL-6 assay, in which labeled strepavidin binds biotin-labelled anti-IL-6 antibodies, the "tracer" is the biotin labeled antibody which enables subsequent detection via the peroxidase labeled strepavidin in a colorimetric test. In this case, the tracer can be the specific binding partner of the analyte. Accordingly, no essential element is seen to be missing from the recitation of claim 1 and the rejection under 35 U.S.C. §112 (second paragraph) should be withdrawn.

With respect to claim 6, it is intended that that claim refers to multiple separate assays performed in parallel in a multiwell plate, for example. Use of such multiwell plates is well known in the art to perform multiple assays in individual wells simultaneously and is described on page 13, lines 4-8 and in the examples such as Example 1. While different types

of assays requiring different types of detection equipment would typically not be carried out simultaneously, samples from the same or different sources could be assayed simultaneously. With respect to claims 8, 9, 10, 15 and 16, the assay steps of those claims all relate to the nature of the specific binding or signal detection mechanisms of those claims. Accordingly, the rejection of claim 6 should be withdrawn.

The rejections of claims 17 and 18 should be withdrawn in light of the amendment of those claims to provide antecedent basis.

B. The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

The rejection of claims 1, 2, 4, 5, 8-11 and 13-20 over Cook (1) in view of Lundin under 35 U.S.C. §103(a) should be withdrawn because one of ordinary skill in the art and lacking the hindsight knowledge of Applicant's invention would not have been motivated to pick and choose from the art in a manner which would have arrived at Applicant's invention.

Starting with the disclosure of Cook (1), the worker of ordinary skill, in arriving at the present invention, would have been faced with a number of choices. Thus, starting with Cook (1) many forms of SPA, including those which utilize specific binding assays, are generally disclosed. Cook (1), however, does not disclose the use of SPA or specific binding assays with lysed cellular samples.

Thus, the skilled worker was faced with a first choice: can specific binding assays be carried out in lysed cellular samples? Cook did not give any indication of whether such an approach would be successful. If, however, the skilled worker made the correct choice, he or she would have been faced with a situation where a cell lysis agent would be present in the reaction mixture. Cook (1) did not address this issue.

Thus, the skilled worker would again would be faced with a choice, specifically as to whether the presence of detergent would pose a problem for specific binding assays. Neither Cook (1) or (2) addressed this situation. Lundin did address this issue, however, only to the extent of pointing out the problematical effect of detergent on enzymes in enzyme assays. None of the prior art documents raised or addressed the issue of negative interactions between detergent and components of a specific binding reaction. The Applicant, in making a second choice, recognized that this was an issue and addressed it. The invention resulted, in part, from recognition of this problem which was not identified or addressed by the cited art.

At that stage, the Applicant had made a number of choices to arrive at a situation whereby a specific binding assay was being used to assay for analyte from a lysed cellular sample whereby a cell lysis agent present in the reaction mixture was recognized to represent a potential problem. In addressing this perceived issue, the Applicant made a further choice to use cyclodextrins as a means of neutralizing the cell lysis agent. While the Action contends that this affirmative choice was rendered obvious by the availability at the time of the contents of Lundin which teaches the use of such a lysis agent/neutralizing agent in an ATP catalysed enzyme assay, the choice is not so straightforward.

Specifically, the complexing problems inherent with the use of cyclodextrins, as highlighted by Lundin, taught away from the present invention by providing compelling reasons against the use of cyclodextrins in the specific binding reactions claimed by the present application. Thus, Lundin appeared to hint at the potential complexing problems inherent in the use of certain types of cyclodextrins (Col. 7, lines 52-60) where the problem was overcome by increasing the amount of the complexed agent (D-Luciferin). While this problem could be overcome in an enzyme assay where the complexed agent was not the intracellular agent to be measured, the use of a similar solution would not have been applicable in the present invention

as the agent being complexed would predictably be one of the intracellular components to be measured. In view of this, it would appear that the teaching of Lundin (that of the use of a cyclodextrin sequestrant in firefly luciferase enzyme assays) would not be expected by the skilled person to be applicable to specific binding assays. Indeed, those of skill in the art, when faced with knowledge of Lundin's teaching, would not have attempted a specific binding assay using a complexing agent as strong as cyclodextrin as a sequestrant.

This is because the presently claimed assays measure the specific binding reaction itself whereas Lundin described assaying for ATP in a luminescence assay where ATP merely acts as a co-factor in an enzyme catalyzed luciferase reaction. Such an enzyme reaction is effectively an amplification step; thus, even if some complexing to ATP occurs, a small amount of ATP will still be detectable by forcing the dynamics of the enzyme catalyzed reaction. This was suggested in Lundin (see Col. 7, lines 56-60) where it was stated that the complexing problem "could be obviated by increasing the concentration of D-luciferin" and that "if an apparent inhibition is found in any other assay it is recommended to optimise the concentrations of all co-factors in the presence of the cyclodextrins to be used."

In contrast to Lundin, the claimed assay measures the specific binding reaction *per se* (refer, for example, to labelled cAMP being displaced from its specific antibody). Any complexing effect of a cyclodextrin in this assay could not be compensated for by optimizing the concentrations of cofactors etc. because there is no such amplification reaction. Thus, any complexing effect would have a direct impact on the amount of binding that could be detected.

For these reasons, the rejection of claims 1, 2, 4, 5, 8-11 and 13-20 over Cook (1) in view of Lundin should be withdrawn.

Moreover, the rejection of claims 6, 7 and 12 over the combination of Cook (1), Lundin and Cook (2) should also be withdrawn for the reasons set out with respect to claim 1

above. While Cook (2) discloses various elements of the dependent claims including use of a multiwell system, it does not make up for the deficiencies of Cook (1) and Lundin in teaching the subject matter of independent claim 1. Accordingly, the rejection of claims 6, 7 and 12 should also be withdrawn.

CONCLUSION

In light of the foregoing amendments and remarks, it is believed that claims 1, 2 and 4-20 are in condition for allowance and a notice thereof is respectfully requested. Should the Examiner wish to discuss any further matter of form or substance, she is encouraged to contact undersigned attorney at the telephone number listed below.

Respectfully submitted,

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VERSION WITH MARKING TO SHOW CHANGES MADE

In the Claims:

Claims 17 and 18 have been amended as follows:

17. [AMENDED] The method as claimed in claim 1, wherein the [assay reagents] reaction mixture comprises a tracer.

18. [AMENDED] The method as claimed in claim 1, wherein the [assay reagents] reaction mixture comprises a labeled reagent for detection wherein the label is selected from the group consisting of radioactive isotope labels, enzyme-linked labels and fluorescent labels.